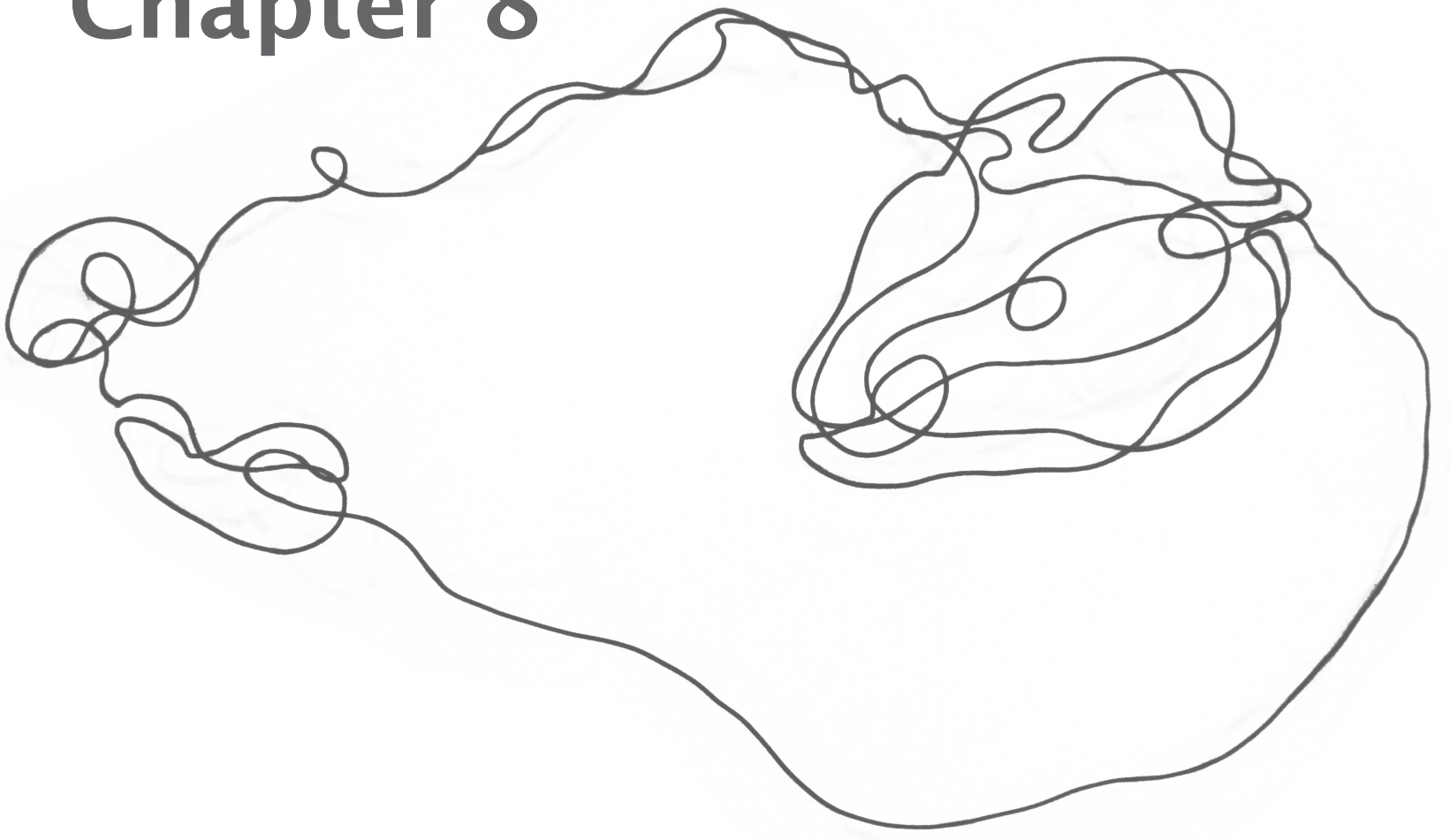
Chapter 8



Diuretic response and resistance in acute heart failure: pathophysiology, evaluation and therapy

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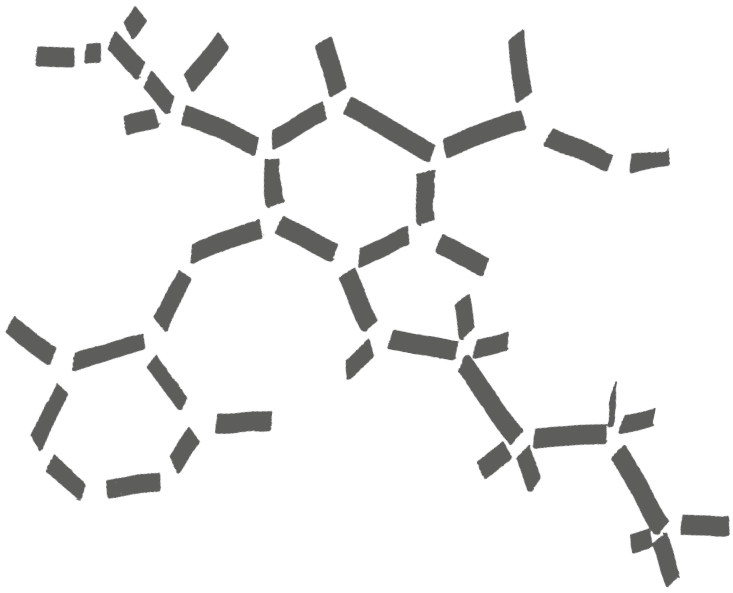

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Summary

Administration of loop diuretics to achieve decongestion is the cornerstone of acute heart failure therapy. Unfortunately, impaired response to diuretics is common and associated with adverse outcomes. Diuretic resistance is thought to result from a complex interplay between cardiac and renal dysfunction and specific renal adaptation and escape mechanisms. However, our understanding of diuretic response in acute heart failure is still limited and a uniform definition is lacking. Several strategies have been proposed to overcome diuretic resistance, including combination therapy and ultrafiltration, but prospective studies in truly unresponsive patients are lacking. A better understanding of diuretic response should ultimately lead to a better, individualized approach to treating patients with acute heart failure.

Abbreviations

ADH	Anti-Diuretic Hormone, arginine vasopressin
AHF	Acute Heart Failure
BUN	Blood Urea Nitrogen
ECV	Extracellular Volume
GFR	Glomerular Filtration Rate
MRA	Mineralocorticoid Receptor Antagonist
OAT	Organic Anion Transporter
RAAS	Renin-Angiotensin-Aldosterone System

Introduction

Acute heart failure (AHF) is one of the leading causes of hospital admission worldwide, and is associated with high morbidity, mortality and high rehospitalization rates.[1, 2] Most of the symptoms associated with acute heart failure are the result of excessive fluid retention, and loop diuretics are the treatment of choice to combat them. Loop diuretics are administered in up to 90% of patients hospitalized for acute heart failure, despite the lack of evidence for outcome benefit.[2, 3] Poor response to diuretics - persistent signs and symptoms despite adequate diuretic therapy, called diuretic resistance – frequently occurs during hospitalization for acute heart failure. In two recent studies, a poor response to diuretics was more frequently found in patients with diabetes, lower glomerular filtration rate (GFR), higher blood urea nitrogen (BUN) levels and a lower systolic blood pressure. Importantly, a poor diuretic response was independently associated with less symptom relief and a higher risk of in-hospital worsening heart failure, and increased post-discharge mortality and three times higher rehospitalization rates.[4, 5] In an accompanying editorial, Braunwald stressed the importance of diuretic resistance and called upon better definition and quantification of diuretic response to loop diuretics.[6] However, the pathophysiology behind diuretic resistance is not completely understood, but is thought to result from the complex interplay between cardiac and renal dysfunction and specific renal adaptation and escape mechanisms. This review will address the pathophysiologic background of diuretic resistance, the evaluation and definition of diuretic response, and current and future strategies aimed at improving diuretic response.

Pathophysiology

Cardiorenal interplay

Heart and kidney act in concert, regulating circulatory homeostasis through several mechanisms and feedback loops. In healthy individuals, glomerular filtration remains stable despite changes in volume and blood pressure. When triggered by sodium and volume overload, a rise in atrial pressure and release of natriuretic peptides facilitates renal sodium excretion via direct tubular effects and an increase in glomerular filtration rate.[7-9] Concomitant suppression of the renin-angiotensin-aldosterone system (RAAS) contributes to stable blood pressure via systemic vasodilation and renal sodium excretion by inhibiting the tubular effects of angiotensin II and aldosterone.[10] In contrast, in a volume depleted state, increased RAAS activity contributes to maintenance of blood pressure and renal sodium retention. Furthermore, angiotensin II induces renal efferent vasoconstriction, helping maintain renal filtration pressure and filtration rate despite decreasing arterial pressure. Sympathetic nervous system activation mirrors that of the RAAS. Moreover, the cardiorenal interaction affects osmoregulation via effects on water diuresis. Under physiological conditions, the release of arginine vasopressin (antidiuretic hormone, ADH) is stimulated by a high plasma osmolarity.[11] The ensuing renal water reten-

tion restores normal osmolarity. However, during pronounced volume disturbances, responses to volume depletion or overload can overrule the osmotic triggers, contributing to restoration of volume status at the expense of osmoregulation.

In acute heart failure, a decrease in cardiac function causes reduced cardiac output and arterial underfilling, leading to decreased activation of arterial stretch receptors, resulting in compensatory systemic and intrarenal vasoconstriction.[12] Decreased stretch of the glomerular afferent arteriole stimulates renin release, which leads to angiotensin II production. Angiotensin II causes afferent and efferent vasoconstriction, stimulates sodium retention in the proximal tubule and aldosterone release.[13] In turn, aldosterone increases sodium reabsorption in the collecting duct, resulting in extracellular fluid expansion and systemic congestion.[14] Normal, healthy subjects display an aldosterone escape mechanism, with sodium delivery to distal renal tubules caused by increased vascular volume overcoming the sodium retaining effect of aldosterone; this mechanism is impaired in heart failure patients, where reduced renal blood flow forces continued sodium retention in response to aldosterone.[12, 15]

Heart failure also causes baroreceptor-mediated sympathetic nervous system activation that promotes vasoconstriction and contributes to further RAAS activation and renal sodium and water retention.[16] ADH release exacerbates these effects.[17] Additionally, the protective effect of natriuretic peptides is diminished in AHF due to renal vasoconstriction, reduced sodium delivery, less active forms of natriuretic peptides and down-regulation of their receptors.[18, 19] The combination of the pathways described above creates a vicious circle that causes congestion and worsening heart failure.

A major symptom of heart failure is decreased organ perfusion. The kidney can compensate for a drop in renal blood flow by increasing the filtration fraction via the abovementioned angiotensin II-mediated efferent vasoconstriction, thus preserving GFR.[20] The combination of pump failure, neurohormonal activation and heart failure therapies – particularly angiotensin-converting enzyme inhibitors and angiotensin receptor blockers – can eventually overcome the kidney's ability to compensate for reduced perfusion.[21, 22] Additionally, increased venous filling and abdominal pressures caused by ascites can increase renal afterload and intrarenal pressure, reducing the transrenal perfusion gradient (and thus renal perfusion pressure), increasing renal interstitial pressure (directly opposing filtration pressure) and contributing further to renal insufficiency.[23-25]

Mechanisms of diuretic resistance

Diuretics are the first-line therapy for volume overload resulting from these mechanisms, and aim to establish a negative sodium and thus fluid balance. Poor response to diuretics is an important clinical problem in patients with acute heart failure and its underlying pathophysiologic mechanisms are diverse.[2, 26]

Regulation of renal sodium excretion involves several sequential transport mechanisms in the renal tubule. Diuretics act on specific transport mechanisms, and are classified based on their tubular site of action (Figure 1). Acetazolamide and mannitol act on the proximal tubule, where up to two-thirds of the sodium load is filtered under physiologic conditions. Acetazolamide produces alkaline diuresis via bicarbonate excretion with sodium and potassium by inhibiting carbonic anhydrase in the proximal tubule.[27] Mannitol is an osmotic diuretic that acts primarily on the loop of Henle and the proximal tubule by increasing the osmotic pressure of glomerular filtrate, thus inhibiting tubular reabsorption.[28] Loop diuretics inhibit the Na+/2Cl-/K+ co-transporter in the thick ascending limb of the loop of Henle, causing decreased sodium and chloride reabsorption from the urine.[29] Thiazide diuretics act on the distal convoluted tubule by blocking the sodium chloride transporter in the distal tubule. Metolazone is a thiazide-like diuretic that exhibits its effect in the distal tubule by inhibiting the reabsorption of sodium and chloride ions.[30] Aldosterone antagonists (mineralocorticoid receptor antagonists) act on the collecting duct by competitively antagonizing the aldosterone receptor, thereby reducing sodium reabsorption.

Delivery of diuretics to the site of action relies on several mechanisms (Figure 2). First, orally administered diuretics first have to be absorbed in the gut to enter the bloodstream. In the presence of gastro-intestinal edema or gut hypoperfusion, absorption of orally administered diuretics is impaired, and may differ significantly between diuretics.[31] For example, bumetanide absorption is likely better than that of furosemide under these circumstances. Intravenous administration can overcome impaired absorption of orally administered diuretics. In patients with renal insufficiency and heart failure, a higher diuretic dose is required to achieve the same effects, and increasing diuretic doses will be less effective.[26]

Second, most loop diuretics (though interestingly not bumetanide), thiazide diuretics, metolazone and acetazolamide are bound to plasma albumin and act on their molecular target from the luminal side, meaning that they must be filtered by the glomerulus and actively secreted into the tubular lumen by the proximal tubule's organic anion transporter (OAT) in order to function.[32, 33] Hypoalbuminaemia, common in heart failure patients, impairs uptake and secretion of active furosemide and enhances conversion to its inactive form.[34, 35] Additionally, albumin lost into the tubule may bind furosemide and prevent it from acting on the Na+/2Cl-/K+ co-transporter.[36, 37] Co-administration of albumin and furosemide improves diuretic response in patients with cirrhosis, nephrotic syndrome or chronic kidney disease, but no data are available in heart failure.[38-40]

Third, patients with heart failure and chronic renal dysfunction have elevated levels of circulating organic acids, like BUN, which competitively inhibit the OAT and further reduce diuretic availability at the site of action.[41, 42] RAAS and sympathetic nervous system activation cause flow-dependent passive resorption of urea in the distal tubule; a concentration gradient created by increased sodium and water resorption in the proximal tubule results in diminished distal flow and increased

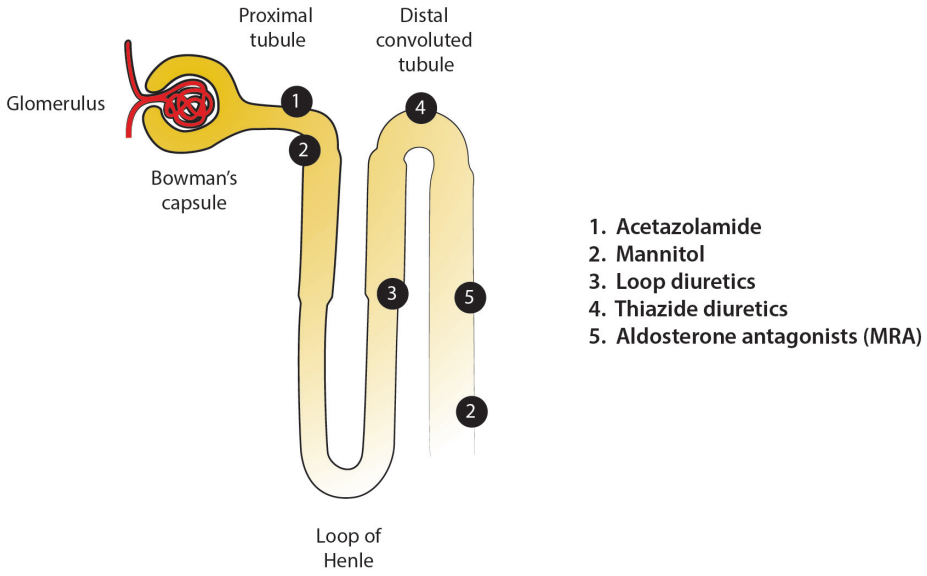

Figure 1 Sites of action for diuretic and alternative therapies

reabsorption.[43, 44] High circulating BUN levels therefore not only contribute directly to diuretic resistance, but also reflect a kidney actively working to retain sodium and water. Thus, in patients with heart failure, impaired absorption, decreased renal blood flow, azotemia, hypoalbuminemia and proteinuria – resulting in reduced levels of active diuretics in the tubular lumen - may affect diuretic effectiveness.

At the onset of diuretic treatment, the natriuretic effect results in the intended negative sodium balance. The resulting decrease in extracellular volume (ECV) triggers a homeostatic response, mediated by activation of the RAAS and the sympathetic nervous system, leading to increased sodium retention at tubular sites not targeted by the specific diuretic.[45, 46] After several days, this homeostatic response counterbalances the diuretic effect of the drug, balancing sodium excretion and intake, and creating a new steady state with a lower ECV. This "braking phenomenon" is an appropriate homeostatic response that prevents excessive volume depletion during continued diuretic therapy. However, in conditions with pre-existent secondary hyperaldosteronism, such as heart failure, this phenomenon can be very pronounced and contribute to diuretic resistance.[47] Furthermore, persistent delivery of sodium or diuretics to the distal tubule causes hypertrophy of the distal tubular cells.[48] This bypasses the proximal effect of the loop diuretic and leads to enhanced sodium retention. Other non-cardiac mechanisms causing a diminished response to diuretics, including reduced renal blood flow caused by renal artery stenosis or drug-drug interactions, should also be considered.[29]

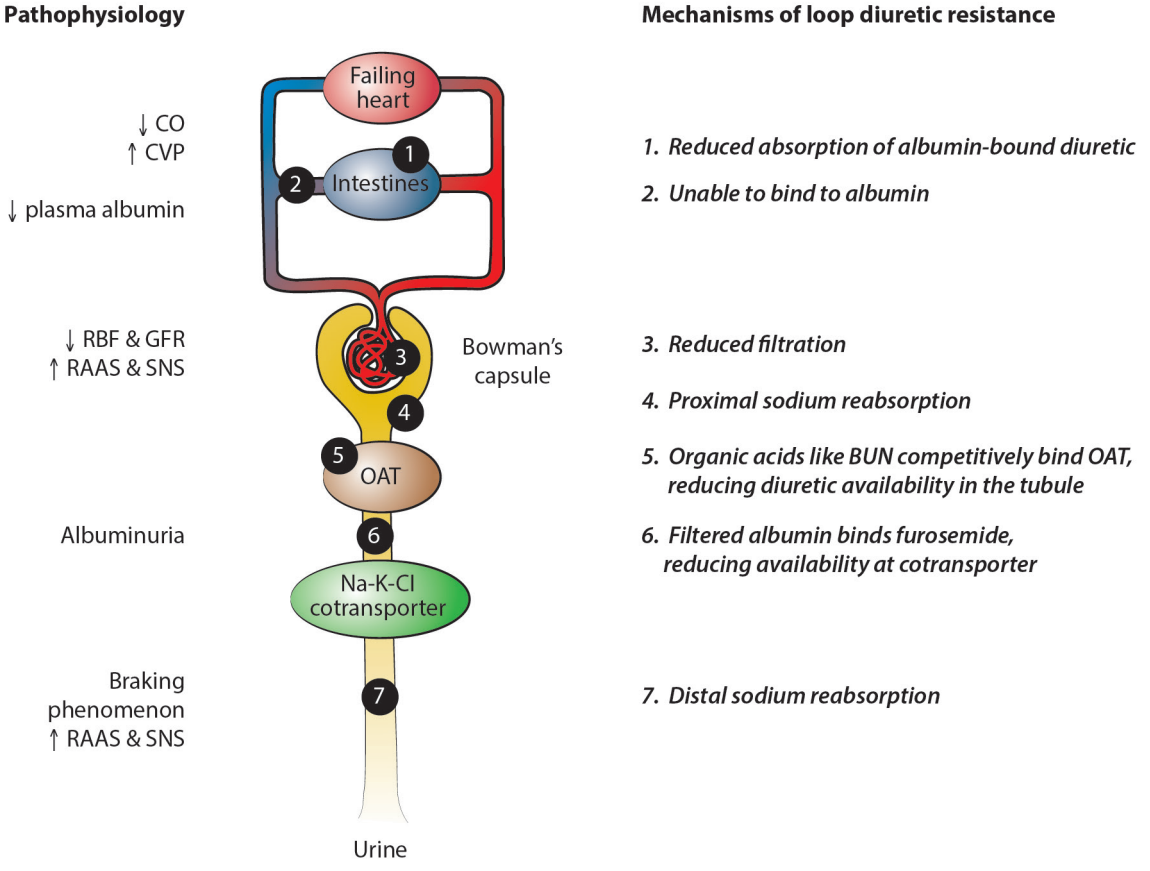

Figure 2 Pathophysiology and mechanisms of loop diuretic resistance

How to evaluate diuretic response and resistance?

There is no single accepted definition of diuretic resistance. Several have been proposed, the most frequently mentioned being "failure to decongest despite adequate and escalating doses of diuretics." Less clinically applicable definitions have also been suggested (Table 1). In clinical practice, unresponsiveness to diuretics leading to persistent signs and symptoms of congestion is usually considered diuretic resistance. Three objective methods to evaluate diuretic response have recently been introduced (Table 2). These measures suggest diuretic response should be determined based on the effect of diuretic dose administered.

Table 1 Definitions of diuretic resistance

Persistent congestion despite adequate and escalating doses of diuretic (>80 mg furosemide/day)	Neuberg et al.[89]
Fractional sodium excretion (amount of sodium excreted as a percentage of filtered load) of <0.2%	Knauf et al.[90]
Failure to excrete at least 90 mmol of sodium within 72 hours of a 160 mg oral furosemide dose given twice daily	Epstein et al.[91]

Valente et al. investigated a quantitative measure of diuretic response, combining decongestive effect and diuretic dose.[4] Diuretic response was defined as weight loss per 40 mg furosemide (or equivalent). A poor diuretic response independently predicted heart failure rehospitalization and mortality. This metric was recently investigated in RELAX-AHF, confirming these findings.[49] Using weight change per unit of furosemide may provide an applicable metric to confirm the clinician's impression that a patient is resistant to diuretics. Testani et al. used similar metric to define diuretic response, termed diuretic efficiency, defined as net fluid loss per mg of loop diuretic (40 mg of furosemide or equivalent) during hospitalization for acute heart failure, dichotomizing above and below the median.[5] Consistently with results by Valente et al, low diuretic efficiency was associated with worse long-term outcomes. In both studies, poor diuretic response or efficiency was associated with renal impairment and higher BUN levels. However, diuretic response is not only a reflection of renal impairment; poor diuretic response was also associated with more advanced heart failure, diabetes and atherosclerotic disease.

More recently, Singh et al examined a ratio of urinary sodium to urinary furosemide, measured in spot urine samples. A poor response (< 2 mmol/mg) was associated with impaired clinical outcome, independently of renal function.[50] Hemoconcentration has also been suggested as a practical and readily applicable strategy to assess diuretic response.[51] Ultimately, following more extensive validation and investigation, use of such diuretic response metrics could be used to help identify patients who might benefit from alternative decongestive therapies and guide treatment selection.

Table 2 metrics of diuretic response

Weight loss on day 4 divided by administered unit of 40 mg furosemide (or equivalent) on days 1-3	Valente et al.[4] Voors et al [49]
Net fluid loss per mg of loop diuretic (40 mg of furosemide or equivalent) during hospitalization	Testani et al.[5]
Natriuretic response to furosemide as the ratio of urinary sodium to urinary furosemide	Singh et al.[50]

Treatment of diuretic resistant patients

Several strategies have been proposed to overcome diuretic resistance (Figure 3). First, non-compliance should be ruled out by verifying mediation intake and sodium restriction.[26] Second, non-steroidal inflammatory drugs (NSAIDs) should be discontinued, because they potentially cause diuretic resistance by inhibiting cyclo-oxygenase and thus interfering with prostaglandin synthesis, which antagonizes the natriuretic response to loop diuretics.[52] Third, switching loop diuretics may be useful. Bumetanide and torsamide, for example, have higher biological absorption compared to furosemide in CHF patients.[31, 47] In the TOrasemide In Congestive heart failure (TORIC) study in outpatients with CHF, torasemide treatment was associated with a lower mortality and a significant improvement in NYHA class compared to furosemide or other diuretics.[53] A recent small meta-analysis confirmed these findings, suggesting a trend toward improvement in NYHA class and mortality with torsamide treatment.[54] Fourth, efficacy of diuretic therapy can be improved by switching from oral to intravenous administration to circumvent impaired enteral drug uptake in congested patients. Several smaller studies have suggested that continuous infusion improves diuresis, renal function and leads to fewer adverse events compared to bolus injections.[55-57] However, the Diuretic Optimization Strategies Evaluation (DOSE) trial found no differences in either treatment response or outcome in patients randomized to bolus versus continuous infusion, although diuretic doses and the incidence of worsening renal function were higher in the bolus group.[58]

Combined diuretic therapy

If escalating (intravenous) doses of loop diuretics are insufficient, combination therapy with two classes of diuretic drugs may improve diuretic efficacy. The addition of a thiazide diuretic enhances sodium excretion via several mechanisms, including inhibition of distal sodium reabsorption.[59] As thiazides have a longer half-life, they prevent post-diuretic sodium retention after cessation of loop diuretic activity.[29] Potential dangers of combination therapy include hypokalaemia, hyponatraemia, dehydration, worsening renal function and metabolic acidosis; therefore,

careful monitoring is required.[60] Addition of metozalone to a loop diuretic results in marked diuresis and is especially useful in patients with renal failure, since metozalone is able to produce diuresis despite a low GFR.[61, 62]

Since a large amount of sodium is reabsorbed in the proximal tubule, adding a proximally acting diuretic may be beneficial. In healthy volunteers, addition of acetazolamide to furosemide showed a minor additive effect.[63] Khan et al reported an additional effect of acetazolamide in terms of correcting metabolic acidosis and increased diuresis when used intermittently in combination with furosemide and spironolactone therapy in congestive heart failure.[64] As acetazolamide is cleared renally, caution is recommended in patients with advanced renal failure due to the risk of concentration-dependent side-effects. Another option is mannitol; Turagam et al reported effective diuresis in 80.3% of acute heart failure patients treated with furosemide-mannitol infusion, though the study had no control group.[65] To date, studies evaluating combination therapy in (diuretic resistant) heart failure patients are scarce and evidence remains inconclusive. Two trials (DIURESIS-CHF, clinicaltirals.gov no. NCT01973335 and CLOROTIC, clinicaltrials.gov no. NTCT01647932) investigating combination therapy are respectively ongoing and planned. Neither study explicitly defines diuretic resistance as a inclusion criterion. Adding a natriuretic dose of mineralocorticoid receptor antagonist (MRA) to diuretics may also help overcome diuretic resistance by blocking the aldosterone receptor and thus preventing excess sodium reabsorption in the collecting duct caused by secondary hyperaldosteronism.[66] MRAs at low doses are guideline-recommended therapy in heart failure and significantly improve survival.[1, 67, 68] The randomized aldactone evaluation study (RALES) dose-finding study revealed that higher doses of spironolactone (50-75 mg daily) had natriuretic effects.[69] In two relatively small, single centre studies, addition of high dose spironolactone was associated with increased diuresis or earlier resolution of symptoms and signs of congestion.[70, 71] A common side-effect of high dose MRAs is hyperkalaemia; new MRAs with a lower potential for causing electrolyte disturbances are currently being investigated.[72, 73]

Dopamine

Addition of low dose dopamine to diuretic therapy has been suggested as a way to improve renal blood flow and thus preserve renal function and improve diuresis.[74] The Renal Optimization Strategies Evaluation (ROSE) trial tested two independent hypotheses – that addition of low dose dopamine or low dose nesiritide, compared with placebo, to diuretic therapy will enhance decongestion and preserve renal function in patients with acute heart failure and renal dysfunction.[75] However, neither dopamine nor nesiritide had a significant effect on urine volume or change in Cystatin C, suggesting no added benefit to diuretic therapy. More recently, the prematurely discontinued, small-scale Dopamine in Acute Decompensated Heart Failure II (DAD-HF II) trial confirmed these findings, despite promising results in DAD-HF I.[76, 77] The results of these studies suggest dopamine does not improve diuretic response in acute heart failure.

Ultrafiltration

Ultrafiltration is an effective method for fluid removal that filters plasma water directly across a semipermeable membrane using a pressure gradient.[78] This yields an ultrafiltrate that is iso-osmotic compared to plasma. Several studies comparing the efficacy and safety of ultrafiltration to diuretics in heart failure have been conducted in recent years. Two randomized controlled trials comparing diuretic therapy to ultrafiltration, the Relief for Acutely Decompensated Congestive Heart Failure (RAPID-CHF) and the Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure (UNLOAD) found greater fluid removal in the ultrafiltration group, though weight loss after 24 hours did not differ in the former and dyspnea scores were similar in the latter.[79, 80] Interestingly, ultrafiltration was associated with significant reductions in heart failure rehospitalization and fewer unscheduled visits. The Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) examined the use of ultrafiltration in AHF patients with cardiorenal syndrome.[81] Patients were randomized to stepped diuretic therapy or fixed-rate ultrafiltration. Ultrafiltration was inferior to pharmacological therapy, primarily due to an increase in the creatinine level in the ultrafiltration group, along with more adverse events. It must be noted that not all patients in the ultrafiltration group received ultrafiltration therapy, and that the rate of fluid removal in the ultrafiltration arm has been questioned. So far, ultrafiltration has not been studied specifically in diuretic resistant patients. Multiple studies on ultrafiltration in heart failure are ongoing, while a recent phase III outcome trial (AVOID-HF, clinicaltrials.gov NCT01474200) was terminated due to recruitment problems. Unfortunately, none of the ongoing studies explicitly address diuretic resistance.

Alternative therapies

Various intravenous agents have been investigated in acute heart failure, and although none have shown convincing survival benefits to date, several have mechanisms of action that may be helpful in overcoming diuretic resistance. Tolvaptan (a vasopressin V_2 receptor blocker) is effective in increasing sodium concentrations in patients with hyponatremia, increases urine output in patients with symptomatic heart failure and may therefore have additive value in diuretic resistant patients.[82, 83]

Several synthetic natriuretic peptides have been developed and investigated in heart failure. Nesiritide, a synthetic B-type natriuretic peptide approved for symptom relief by the FDA, but not by European regulators due to lack of efficacy, did not increase urine output in patients with acute heart failure, and is therefore unlikely to have additive value in patients with diuretic resistance.[84] Ularitide is a synthetic form of urodilatin, a human endogenous natriuretic peptide that is expressed in the kidney and induces natriuresis and diuresis by binding to specific natriuretic peptide receptors.[85] It may have therapeutic advantages in acute heart failure and specifically in diuretic resistant patients. The Efficacy and Safety of Ularitide for the Treatment of Acute Decompensated

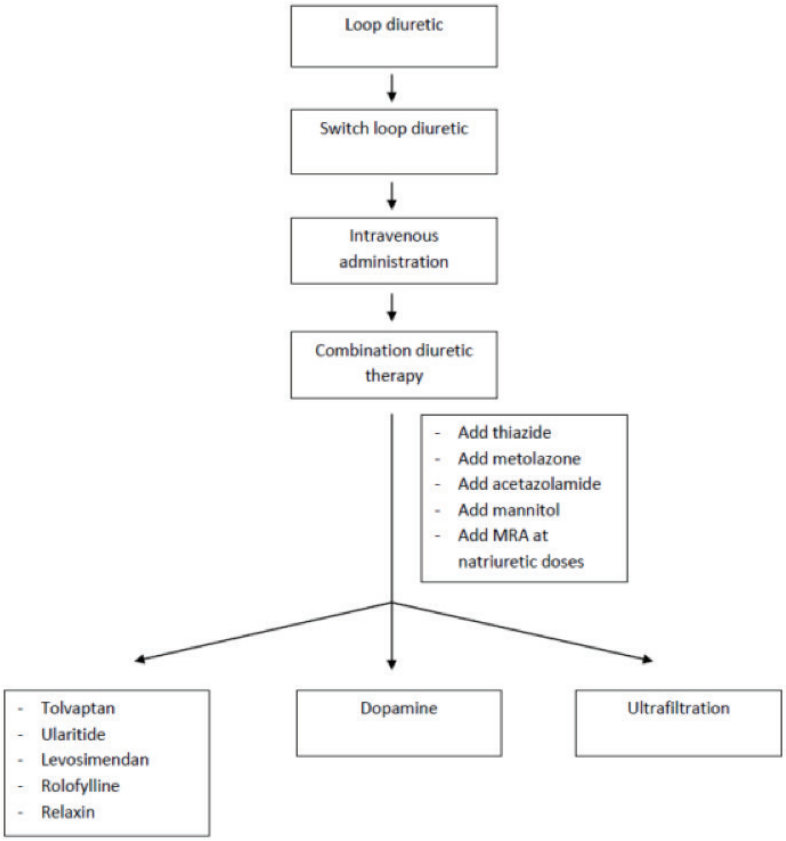

Figure 3 Strategies for overcoming diuretic resistance

Heart Failure trial (TRUE-AFH; clinicaltrials.gov no. NCT01661634) is ongoing. Levosimendan is a phosphodiesterase inhibitor with vasodilator and positive inotropic properties that provides rapid and durable symptom relief and has positive effects on renal function, and could therefore help treat symptoms in diuretic resistant patients.[86]

A small study suggests that addition of prednisone in patients with diuretic resistance results in marked diuresis and improved renal function.[87] Further studies are needed to confirm these findings.

As shown by Valente et al, treatment with the adenosine A-1 antagonist rolofylline was a significant predictor of diuretic response due to greater weight loss, possibly due to improved renal perfusion or direct diuretic effects.[4] In a specific subset of patients, adenosine A-1 inhibition may help overcome diuretic resistance, although

the side-effect profile of rolofylline, in addition to lack of efficacy, led to discontinuation of its development. Serelaxin is a human recombinant of the vasodilator relaxin-2, with systemic and renal effects. Though no significant effect of serelaxin on diuretic response was observed, it may be that its beneficial effects are related to prevention of organ damage.[49, 88]

Conclusions and future perspectives

Impaired diuretic response is a common problem in patients with acute heart failure and strongly associated with poor in-hospital and post-discharge clinical outcomes. Recently, quantitative measures for diuretic response were proposed but need to be validated in other acute heart failure populations. In addition to establishing the value of diuretic response metrics as prognostic markers, early identification of patients at risk of a poor response may allow initiation of therapies aimed at modifying response. Prospective studies using a validated diuretic response metric to identify diuretic resistant patients are a necessary first step towards identifying the best strategies for overcoming diuretic resistance, and determining whether this leads to improved outcomes. This could ultimately result in a better, individualized approach to treating the acutely decompensated heart failure patient, for whom no evidence based therapies exist.

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